REMARKS

Status of the Claims

Claims 1-15 are pending as shown above and claims 2-5 are under active examination.

Drawings

Submitted herewith are replacement drawings.

35 U.S.C. § 112, 1st paragraph, written description

Claims 2-5 were rejected under 35 U.S.C. § 112, 1st paragraph as allegedly containing new matter for reciting an array of polynucleotides "consisting of accessible regions of cellular chromatin." (Office Action, paragraph 5). In addition, it was alleged that because the sequence listing includes a single sequence, the specification fails to describe multiple "accessible regions of cellular chromatin" and probes used to isolate the members of the array (Office Action, paragraphs 6 and 7). It was further alleged that the claimed arrays can encompass any "available" nucleic acids. (Office Action, paragraph 8, citing page 8 of the specification). It was also alleged that because an array as claimed is not exemplified, the written description requirement is not satisfied. (Office Action, paragraphs 9-12). Finally, it was alleged that the applicant is attempting to satisfy written description via obviousness. (Office Action, paragraphs 13 and 14).

As a threshold matter, Applicants note that many of the same rejections were raised previously in an Office Action dated Mary 28, 2008 and addressed in a Response filed August 28, 2008. As indicated in the Final Office Action mailed February 26, 2009, all the rejections were withdrawn in view of Applicants' arguments. Therefore, Applicants again traverse the rejection and supporting remarks and address each in turn.

1. No new matter was added by the previous amendment

The proscription against the introduction of new matter in a patent application (35 U.S.C. §§ 132 and 251) serves to prevent an applicant from adding information that goes beyond the subject matter originally filed. See, e.g., *In re Rasmussen*, 650 F.2d 1212, 1214, 211 USPQ 323,

326 (CCPA 1981) and MPEP § 2163.06. However, literal description of claimed subject matter is never required (M.P.E.P. § 2163.02):

> The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement.
>
> Thus, the written description requirement is satisfied if the specification reasonably conveys possession of the invention to one skilled in the art. See, e.g., *In re Lukach*, 169 USPQ 795, 796 (CCPA 1971).

Second, the disclosure must be read in light of the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to patents and publications available to the public prior to the filing date of the application. See, e.g., *In re Lange*, 209 USPQ 288 (CCPA 1981). Not only must the disclosure be read in light of the knowledge possessed by one of skill in the art, but the burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in possession of claimed invention at the time of filing. *Vas Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim*, 191 USPQ 90 (CCPA 1976).

Here, the as-filed disclosure and state of the art, establish that the claimed arrays "consisting of accessible regions of cellular chromatin" were clearly described at the time of filing. In this regard, Applicants direct the Examiner's attention to the following passages and working examples of the as-filed specification (page 2, lines 18-21; page 3, lines 7-11; page 12, lines 26-33; page 36, lines 3-5; page 37, lines 30-32; page 40, lines 13-16; page 40, line 31 to page 41, line 3; page 49, lines 2-3, emphasis added):

> Described herein are methods for the use of libraries of regulatory sequences obtained based on accessibility of nucleotide sequences in cellular chromatin. In particular, sequences obtained from such libraries are placed on one or more nucleic acid arrays (e.g., a microarray).
>
> In another aspect, provided herein is an array comprising a plurality of accessible polynucleotide sequences, wherein: (a) the sequences are isolated based on their accessibility in cellular chromatin; and (b) each accessible sequence is located at a distinct address on a solid support. In certain embodiments, the

accessible sequences are isolated from a plurality of different cell types from an organism.

An "accessible region" in cellular chromatin is generally one that does not have a typical nucleosomal structure. As such, an accessible region can be identified and localized by, for example, the use of chemicals and/or enzymes that probe chromatin structure. Accessible regions will, in general, have an altered reactivity to a probe, compared to bulk chromatin. An accessible region may be sensitive to the probe, compared to bulk chromatin, or it may have a pattern of sensitivity that is different from the pattern of sensitivity exhibited by bulk chromatin. Accessible regions can be identified by any method known to those of skill in the art for probing chromatin structure.

As with other embodiments, polynucleotides obtained by the aforementioned methods can be cloned to generate a library of regulatory sequences and/or the regulatory sequences can be immobilized on an array.

As with the other methods, polynucleotides isolated from an immunoprecipitate, as described herein, can be cloned to generate a library and/or sequenced, and/or the sequences can be placed on a nucleic acid array as described in greater detail below.

As disclosed herein, accessible regions can be identified by any number of methods. Collections of accessible region sequences from a particular cell can be cloned to generate a library, polynucleotides from the library, or portions or complements thereof, can be placed on an array...

It will be apparent that certain of the methods described herein can be used in combination to provide confirmation and additional information. For example, treatment of nuclei or cellular chromatin with a probe can be followed by any or all of: isolation of libraries of accessible DNA sequences, mapping the sites of probe reactivity and attaching one or more accessible sequences from the library to an array. Arrays of regulatory sequences are useful in a number of methods, as described below.

As noted above, various techniques can be used to evaluate the library and determine whether it will be used for further purposes such as to make an array.

In addition, pages 24-40 provide detailed description of isolating polynucleotides consisting of accessible regions, while pages 51-54 provide detailed description of array construction. Example 1 shows preparation of a library of 40,000-50,000 clones obtained using a probe for chromatin structure. Example 2 shows detailed analysis of 405 of the obtained clones, including

their regulatory properties, location and the like. Indeed, as shown for one library of human cells, over 90% of sequences were derived from DNAse hypersensitive sites. Given the ample disclosure regarding preparation of accessible region sequences and state of the art regarding preparation of arrays, it is clear that the sequences consisting of accessible regions could be readily placed on an array to make an array consisting of accessible regions of cellular chromatin.

In view of this ample disclosure and working examples, it would be abundantly clear to the skilled artisan that the as-filed specification conveys that Applicants were in possession of the claimed subject matter at the time of filing and no new

2. The specification clearly describes multiple sequences consisting of accessible regions

Satisfaction of the written description requirement does not necessitate that the specification set forth the sequence of every single nucleic acid by structure in the specification. See, *Falkner v. Inglis*, 79 USPQ2d 1001 (Fed. Cir. 2006); *Capon v. Eshhar* 76 USPQ2d. 1078 (Fed. Cir. 2005). Working examples of multiple representative species are also never required to show possession. *Id.* Finally, determining whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to patents and publications available to the public prior to the filing date of the application. See, e.g., *In re Lange*, 209 USPQ 288 (CCPA 1981).

As a threshold matter, Applicants note that, as disclosed in the Examples, approximately 40,000-50,000 clones consisting of accessible regions were actually generated. See, page 62, line 29 of the specification.[1] Furthermore, as noted above and previously, 405 of these clones were further analyzed in a variety of ways. See, Example 2. The written description in this case does not require a listing of the precise sequence of any of the accessible region-containing clones. Rather, all that is required is that the specification evince possession of the polynucleotides forming the claimed arrays. In this case, the specification more than amply meets this requirement in explicit disclosure of a multitude of polynucleotides consisting of accessible

[1] SEQ ID NO:1 as cited in paragraph 6 of the Office Action is not the sequence of an accessible region – it is the sequence of a zinc finger protein.

regions.

3. Working examples of generating individual sequences consisting of accessible regions are provided

Applicants were also clearly in possession of arrays comprising nucleic acid sequences consisting of these demonstrated accessible region sequences. As noted above and on the record, there is detailed description, including working examples, on how to expose cellular chromatin of a cell to a probe that reacts with accessible region sequences of cellular chromatin (but does not react with bulk chromatin) as set forth in step (a) of claim 2. See, e.g., pages 24-40 of the as-filed specification and Example 1. The as-filed specification also amply describes how to identify the cellular polynucleotide sequences that react with the probe such that each cellular polynucleotide sequence consists of an accessible region of cellular chromatin as set forth in step (b) of claim 2. *See, e.g.,* pages 24-40 and Example 2 of the as-filed specification. Furthermore, the as-filed specification provides pages of disclosure on how to attach these sequences to an address on an array. See, Section "V. Arrays" beginning on page 51. It is axoimatic that working examples are never required and, given the ample disclosure regarding identification of sequences consisting of accessible regions and array construction, the skilled artisan would have no doubt that Applicants were in possession of the claimed arrays at the time of filing.

4. The written description requirement is satisfied by the disclosure itself

Finally, contrary to the Examiner's assertion, it is not a reliance on "obviousness" to show that the state art at the time of filing establishes that accessible regions (*e.g.,* isolated as exemplified) could readily be used to form arrays. Rather, as noted above, the written description requirement does not require that the specification reiterate known techniques and, indeed, an applicant should preferably omit what is well known. In the instant case, a myriad sequences consisting of accessible regions are exemplified and described. Furthermore, it is clear from the specification and numerous references are cited in the "Arrays" section that Applicants' were in possession of arrays comprising these sequences.

In sum, there is absolutely no requirement that Applicants exemplify all nucleotide

sequences falling within the scope of the claims in order to adequately describe the claimed arrays. Rather, the test is whether the specification, read in light of the state of the art, contains sufficient disclosure regarding the claimed arrays to satisfy the written description requirement. In the pending case, thousands of sequences were isolated and hundreds characterized. Furthermore, there is clear description in the specification of how to make and use arrays comprising these sequences consisting of accessible regions using conventional molecular biology techniques. Indeed, as previously acknowledged by the Office in withdrawing this rejection, the record establishes that the specification as filed more than adequately describes and details characteristics of the claimed arrays.

35 U.S.C. § 112, 1st paragraph, enablement

Claims 2 to 5 were rejected under 35 U.S.C. § 112, 1st paragraph as allegedly not enabled by the as-filed specification. (Office Action, paragraphs 15-17). U.S. Patent Nos. 6,077,674 (Schleifer) and 5,858,671 (Jones) were cited as allegedly showing unpredictability in making arrays. *Id.*

As with the written description rejection, this enablement rejection was previously made and overcome. Accordingly, Applicants reiterate that the specification is fully enabling for the claimed arrays as made by the claimed methods.

As set forth in the seminal case of *In re Marzocchi,* 439 F.2d, 220, 223, 169 USPQ 367, 369 (CCPA 1971), a patent application is presumptively enabled when filed:

> [a]s a matter of Patent Office practice ... a specification .. must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Moreover,

> it is incumbent upon the Patent Office, whenever a rejection on [grounds of enablement] is made, to explain *why* it doubts the truth

> or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

439 F.2d at 224, 169 USPQ at 369-370. Indeed, as pointed in the Patent Office's own Training Manual on Enablement (1993, citing *In re Wright,* 999 F.2d 1557, 1561-1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993), "the case law makes clear that properly reasoned and supported statements explaining any failure to comply with section 112 are a requirement to support a rejection."

In the instant case, the Examiner has not presented a properly reasoned and supported basis for the rejection. For the reasons presented above with regard to written description, the specification and evidence of record clearly establish that the as-filed specification teaches the skilled artisan how to make and use arrays comprising sequences consisting of accessible regions. The specification also teaches precisely how to isolate sequences consisting of accessible regions based on their altered reactivity to a probe of chromatin structure (e.g., pages 13 and 24-39). Moreover, the specification, in view of the state of the art at the time of filing, teaches how to make arrays comprising these sequences consisting of accessible regions (e.g., pages 51 et seq. and references cited therein) and how to use these arrays for high-throughput screening (e.g., Section VI. Applications beginning on page 55, including for example, identification of binding sites for regulatory proteins, identification of sequence targets, RegDNA chip profiling, chromatin epigenome profiling, etc.). *See, also,* remarks regarding rejection under 35 U.S.C. § 101 below.

In view of the clear disclosure of making arrays by the claimed process steps, the facts and holding in *Genentech v. Novo Nordisk* are inapposite to the pending case. In *Genentech,* the specification lacked "reasonable detail" regarding what is novel, whereas in the pending case there is pages of disclosure as to what is new, namely isolation of sequences consisting of accessible regions. *Genentech* did not require the reiteration of known aspects, but rather that the novel aspects be supplied. Here, attached sequences to an array is a known, not novel aspect and the novel aspect of isolating and identifying sequences consisting of accessible regions without destroying those sequence sequences in the process of identification is fully enabled.

Simply put, there is ample disclosure in the as-filed specification to allow the skilled artisan to make and use the claimed arrays. Exemplification of physically constructing an array is not required to show enablement of the pending claims, as such methods were routine. Indeed, it is well settled that time-consuming or expensive experimentation is **not** undue if it is routine. (See, *e.g.,* PTO Training Manual on Enablement, pages 30-31, citing *United States v. Telectronics Inc.,* USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied* 490 U.S. 1046 (1989) holding the disclosure of a single exemplified embodiment and a method to determine other embodiments was enabling, even in the face of evidence that determining additional embodiments might require 6-12 months of effort and cost over $50,000). Thus, in the instant case, Applicants are not required to actually have exemplified an array as claimed – the disclosure is more than ample to allow the skilled artisan to make and the use the claimed arrays without undue experimentation.

In this regard, the references cited by the Examiner do not in any way establish lack of enablement of the claimed arrays. Jones was filed in 1996, at least 6 years before the effective filing date of the instant application. Schleifer was filed in 1999, 3 years before the case at hand. Thus, these references not indicative of the state of the art regarding arrays at the time of filing. Indeed, the references cited by Applicants regarding arrays, including U.S. Patent No. 6,600,031; 6,326,489; 6,548,021 and WO 02/18648 are much more germane to the state of the art of the regarding array construction.

For the reasons set forth herein, any experimentation needed to make and use the claimed arrays is routine in view of the teachings of the specification and the state of the art. Thus, the Office has not provided sufficient evidence supporting non-enablement and, in the absence of necessary relevant evidence contradicting the teachings of the specification and state of the art, the rejection cannot be maintained.

35 U.S.C. § 101/112

Claims 2 to 5 were rejected under 35 U.S.C. § 101 and § 112 on the grounds that the claimed invention is not supported by a specific, substantial and credible (or well-established) utility based on the assertion that not all nucleic acids have utility. (Office Action, paragraphs

19-23). Again. this rejection was originally set forth in an Office Action mailed May 28, 2008 and withdrawn in a Final Office Action mailed February 26, 2009.

Applicants traverse the rejection and submit that the Examiner is applying an improper standard for compliance with the utility requirement.

In particular, there are three basic utility criteria -- specific, substantial and credible. Alternatively, the presence of a well-established utility is sufficient to meet the utility requirements of 35 U.S.C. § 101/112. Applicants submit that, although they need only satisfy one of these two alternatives, they have provided both specific, credible and substantial utilities, as well as a well-established utility, for the arrays as claimed.

It is well settled that a utility rejection should not be imposed where there is a well-established utility and/or where there is one credible utility (*see,* M.P.E.P. § 2107, emphasis added):

> If at any time during the examination, **it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility**. ...
>
> (1) If the applicant has asserted that the claimed invention is useful **for any particular practical purpose** (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, **do not impose a rejection based on lack of utility**.
>
> ... An applicant need only provide **one** credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement.

Thus, if the applicant has asserted that the claimed invention is useful for any particular practical purpose and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility is improper. Applicants have complied with these standards.

In the pending case, the application sets forth a number of specific uses for the present invention. Here, the claims are not directed to nucleic acids generally. Rather, they are directed to arrays comprising sequence consisting of accessible regions. The utility of arrays that can measure binding to sequences consisting of accessible regions is discussed in detail throughout

the as filed specification, for example on pages 55-61. These utilities includes identification of regulatory proteins, identification of DNA-binding proteins, RegDNA chip profiling, chromatin epigenome profiling, toxicity profiling, SNP interrogation, microRNA validation, drug discovery, expression profiling, etc. These utilities are clearly credible (as well as substantial and specific). Moreover, they are well-established utilities.

It appears that the Examiner will not consider a utility for the claimed arrays in the absence of working examples regarding the arrays *per se*. If this were the standard, the concept of "well known" utility would be meaningless. Applicants submit that they have provided credible, specific and substantial utility, as well as a well-established utility, for the arrays of the present invention.

Based on the foregoing, applicants respectfully submit that the rejections under 35 U.S.C. §101, for lack of utility, should be withdrawn.

35 U.S.C. § 112, 2nd paragraph

Claims 2-5 were rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly indefinite for reciting "accessible regions." (Office Action, paragraphs 25 and 26). As with the written description, enablement and utility rejections addressed above, this rejection is essentially a reiteration of the rejection set forth in the Office Action mailed May 28, 2008 and withdrawn in a Final Office Action mailed February 26, 2009.

Applicants remind the Examiner that the definiteness requirement of 35 U.S.C. § 112, second paragraph is satisfied if it is clear to the skilled artisan what is meant by a particular claim term. *See, e.g., In re Marosi,* 218 USPQ 289 (Fed. Cir. 1983). Further, the definiteness and clarity of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular disclosure; (2) the teachings of the art; and (3) the claim interpretation that would be given by one possessing ordinary skill in the pertinent art at the time the invention was made. *See, e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc.,* 220 USPQ 202 (Fed. Cir. 1983). In other words, the terms at issue must be read in context of the application and field of endeavor.

It is clear from the as-filed specification and state of the art that the terms "accessible region" is sufficiently definite. The definition of "accessible region" found at page 12, line 26 to page 13, line 29 is not "exemplary," but, rather, plainly sets forth that accessible regions of

cellular chromatin are any regions of chromatin that are not bulk chromatin and that a probe is any enzyme or chemical that has altered reactivity with accessible chromatin as compared to bulk chromatin. See, also, page 24, line 29 to page 25, line 8 of the as-filed specification:

> The accessibility of DNA in chromatin refers to any property that distinguishes a particular region of DNA, in cellular chromatin, from bulk cellular DNA. See, for example, Wolffe "Chromatin: Structure and Function" 3rd Ed., Academic Press, San Diego, 1998 for a description of cellular chromatin. For example, an accessible sequence (or accessible region) can be one that is not packaged into nucleosomes, or can comprise DNA present in nucleosomal structures that are different from that of bulk nucleosomal DNA (e.g., nucleosomes comprising modified histones). An accessible region includes, but is not limited to, a site in chromatin at which an enzymatic (e.g., DNAseI) or chemical probe reacts, under conditions in which the probe does not react with similar sites in bulk chromatin. Such regions of chromatin can include, for example, a functional group of a nucleotide, in which case probe reaction can generate a modified nucleotide, or a phosphodiester bond between two nucleotides, in which case probe reaction can generate polynucleotide fragments or chromatin fragments.

Therefore, in light of the specification as a whole, the skilled artisan would clearly be apprises as to the metes and bounds of the claims. Accordingly, the rejection cannot be sustained.

35 U.S.C. § 102(b)

Claims 2 to 5 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 6,153,379 (hereinafter "Caskey") which was cited for teaching arrays of synthesized oligonucleotide primers ranging from about 7 to about 30 nucleotides in length. (Office Action, paragraphs 29 to 32). The Examiner also asserted that Caskey's statement that their array includes "oligonucleotide primers comprising all possible N-mers" was "deemed to meet a limitation of each of claims 2-5." *Id.*

Applicants traverse the rejection and supporting remarks.

The pending claims are drawn to polynucleotide-including arrays in which the polynucleotides consist only of sequences that have been identified as accessible regions of cellular chromatin. Because accessible regions are identified based on altered reactivity to a

probe of chromatin structure (as compared to reactivity of bulk chromatin to that same probe), they cannot possibly be "all N-mers" as described in Caskey. Thus, while the claimed solid surface array may comprise elements in addition to the polynucleotide sequences, each and every polynucleotide sequence on the array consists of a sequence that has been identified as an accessible region.

By contrast, and as acknowledged by the Examiner, the oligonucleotides on Caskey's arrays do not consist of accessible region sequences. The continued insistence by the Examiner that the claims are anticipated by any reference that discloses oligonucleotide arrays is unfounded. In the instant case, the claims are drawn to arrays that comprise a plurality of polynucleotide sequences. Nonetheless, each and every polynucleotide sequence on the array is identified as an accessible region of cellular chromatin (based on altered reactivity to a probe of chromatin structure). Thus, the polynucleotides on the claimed arrays are not random as all of them correspond to an accessible region. Therefore, the claimed arrays are clearly structurally distinguishable (in sequence) from Caskey's "all N-mer" oligonucleotide arrays -- whereas the sequences of the claimed arrays include only accessible region sequences, Caskey's random (or all N-mer) arrays will necessarily include polynucleotides that are non-accessible regions.

Furthermore, the assertion that the polynucleotide sequences on the array can be "from virtually any source" is untenable and not relevant to the claims at issue. Each and every polynucleotide on the array must consist of a polynucleotide that consists of an accessible region of cellular chromatin. Cellular chromatin is not an artificial sequence and, therefore, it does not matter whether the polynucleotide is one that is physically isolated from cellular chromatin or an artificially constructed sequence that mirrors the isolated and identified sequence because all sequences on the array have been identified as accessible regions of cellular (naturally occurring) chromatin.

Therefore, because Caskey does not disclose all the elements of the claims and because the evidence or record clearly establishes that the recited process steps impart structural limitations that distinguish the claims from the arrays of the cited reference, Caskey cannot anticipate any of the pending claims and withdrawal of the rejection is in order.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that all of the pending claims are in condition for allowance and request early notification to that effect.

Should the Examiner have any further questions, Applicants request that the undersigned be contacted at (650) 493-3400.

Respectfully submitted,

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